Study Correlating Lead (Pb) Level Exposure and Bone Shock Absorption Capacity Based on Damping Associated With Higher Modes of Vibration

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Noninvasive vibration testing is one of the tools for characterizing the biomechanical properties of bones and muscle groups in humans and animals. They present alternatives for evaluating bone health quality and may serve as early indicators for bone fragility and bone-related diseases. In recent years, a vibration-based bone shock absorption (BSA) method has shown potential to relate the damping capacity associated with the fundamental (first) vibration modes for developing dynamic bone quality indicators for osteoporosis patients. This research presents a study of early life (birth to age 78 months) lead (Pb) exposure on the damping capacity (bone fragility measures) with the bone shock absorption method. The damping ratio corresponding to few vibration modes is extracted and analyzed using clinical bone shock absorption data of patients with different Pb exposure levels. A method is developed for clustering and identifying three dominant vibration modes and their corresponding damping ratio. The statistical correlation between the damping parameters associated with higher vibration modes and Pb exposure level is presented here. This study highlights the importance of analyzing higher vibration modes and their damping capacity, which could be used to predict early diagnostics precursors of the bone- and/or muscle-related conditions or disorders.

[DOI: 10.1115/1.4050862]

Introduction

Vibration testing and analysis deal with dynamic characterization (estimation of natural frequencies, damping ratios, and corresponding mode shapes) of any biological system or integral elements of the musculoskeletal system such as bones, muscle groups, ligaments, cartilage, collagen/elastin, noncollagenous proteins in the bone mineral complex, water, etc. They characterize the system's dynamic behavior related to their physical parameters such as inertia, stiffness, and damping capacity. Bending natural frequencies and corresponding damping ratios and mode shapes of different human tibiae were obtained from the modal vibration analysis in Refs. [1,2]. The relationship between the natural frequencies and the torsional stiffness of animal bones was established in Ref. [3]. Such characterization allowed correlating variation in vibration parameters to degradation or changes in the mechanical properties of the bone and muscle groups of humans and animals. For example, in Ref. [4], natural frequency measurements on human and animal excised bones indicated reduced bending rigidity in the osteoporotic tibiae compared to the control group. Vibration analysis is being utilized for various research in biomedical sciences and engineering. Natural frequencies are analyzed in Ref. [5] to study fracture healing in bones. The relationship between bone mineral density (BMD) and natural frequencies in the human tibia and its effect on soft tissues was established [6]. The impact of the femur's shape and density on their natural frequencies was studied in Ref. [7], and geometrical parameters were correlated with the natural frequencies and mode shapes of the bone tibia [8]. Additionally, vibration-damping parameters played a crucial role, which is investigated for linking modal damping factor and BMD in sheep femora [9] and developing diagnostic tools for osteoporosis in rats [10].

A noninvasive bone shock absorption (BSA) technique [11] is developed in recent years by the coauthor Bhattacharya and his group. This technique utilizes vibration data obtained from patients' clinical testing and correlates the overall damping parameters obtained at the different anatomical measurement sites with the dynamic bone quality. BSA evaluation provides a "signature" of dynamic bone quality because the measurement of shock-absorption capacity captures an aggregate response of the load-bearing musculoskeletal associated with dynamic active heel-strike. It is shown in Refs. [11] and [12] that statistical analysis of the damping factor associated with the lower extremity bone segment was able to discriminate between patients with and without vertebral fractures. A similar correlation was observed between the damping and dynamic functional postural stability (FPS) and fracture resistance [12]. Traditional dual-energy X-ray absorptiometry (DXA) measurements for BMD alone may not be sensitive enough for quantifying bone fragility (thereby predicting future fracture risk). For example, in some populations, such as children suffering from pediatric bone disorder osteogenesis imperfecta [13], which necessitates new methods of quantifying bone health and predict bone disorder. Hence vibration-based BSA techniques may complement DXA measurements and could offer potentially less invasive and less costly alternatives. These studies have shown that the area under the receiver operating curve (ROC), which are known as AUC values from BSA outcome (damping), ranged between 0.91 and 0.70, while for BMD, it ranged between 0.63 and 0.52 [11,12].

The method employed by Bhattacharya et al. [11–13] analyzed the damping ratio associated with the fundamental (first) mode of vibration corresponding to the first natural frequency, which appears to be around 15–100 Hz for the measurement of lower body extremities. Measured vibration signature from complex structures or biological systems will capture overall dynamics, including lower frequencies (modes) corresponding to softer elements and higher frequencies associated with stiffer components. For example, from experiments, it is found in Refs. [14] and [15] that the human tibia has a first natural frequency significantly higher than the range of 15–100 Hz analyzed in earlier BSA studies. The muscles, ligaments, and other connective tissue contribute to lower stiffness than the encompassed bone; hence their contributions will be reflected in the fundamental frequency. The first vibration mode could also be influenced by the dynamics other than those of the skeletal part, such as postural balance (dynamics of neuromuscular system associated movement of the

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Manuscript received October 18, 2020; final manuscript received April 8, 2021; published online April 26, 2021. Assoc. Editor: Toshihiko Shiraishi.

center of pressure of the whole body), displacement of the joints, or skin-mounted sensors' oscillation, etc. For example, it is observed that soft tissues vibrate at relatively low frequencies, typically below 90 Hz [16]. Therefore, we hypothesize that higher frequencies and their corresponding damping ratios may provide an accurate and consistent association with bone health (stiffer/hard tissues) compared to those obtained for lower frequencies. Hence, to comprehensively characterize bone health concerning its damping capacity, higher modes of vibrations need to be analyzed. An analysis of damping associated with the higher vibration modes and its correlation with the dynamic bone health quality indicators is not available in the literature.

In this research study, clinical data from a BSA study investigating the effect of lead (Pb) on bone health based on vibration signature are analyzed and summarized here. There is sufficient evidence in the literature that exposure to Pb has been shown to detrimentally impact bone health for a prolonged period even after the initial exposure because of its half-life lasting multiple decades. There are numerous pathways through which environmental Pb invades the body, such as breathing, drinking, dermal absorption, to enter the pulmonary system and the blood circulation. The early Pb exposure initially impacts the soft tissue (e.g., neuromuscular system) via blood, affecting vital organs ranging from the central nervous system (CNS), vision, muscles, kidney, and many more [17]. Since Pb has been documented to penetrate the blood-brain barrier, the CNS soft tissues are impacted, damaging structural and functional abilities [18–20]. After causing initial trauma to the soft tissues, Pb deposits in the bone (hard tissues). Pb sequestered in bone continues to reside for decades because of its long half-life, thereby being a source of internal exposure. During hormonal changes associated with pregnancy and menopause, the Pb returns to the blood circulation traumatizing the soft tissues again [21]. Lead pharmacokinetic literature documents that Pb affects osteoclastic and osteoblastic processes, hormonal signaling pathways, and the rate of growth plate chondrocyte maturation [22–25]. Collectively, these potentially contribute to bone fragility and functional postural instability as an added risk of fall-related fractures [26–29]. This paper tests the hypothesis that elevated blood lead levels may be correlated to potential changes to bone quality due to different Pb levels. To the best of our knowledge, no studies are available relating blood lead levels in humans and their effect on bone health.

Therefore, this research deals with a two-pronged investigation, including damping characteristics associated with higher vibration modes and its correlation with dynamic bone quality related to blood Pb levels. The study is targeted to analyze the vibration characteristics (natural frequencies and damping ratio) of the patient data for a range of the spectrum ($\sim$up to 500 Hz.). Steps involving vibration analysis of patient data are presented. Based on the extracted natural frequency and mode pairs, the process, rationale, and results for statistical clustering to identify dominant modes vibration for all patient populations are presented. Subsequently, analysis of variance (ANOVA) analyses to find the correlation between damping capacity associated with the higher vibration modes and patient blood led level is summarized and followed by the conclusions and future direction for this research.

Methods and Results

Subject Profile. In this study, subjects were recruited from the Cincinnati lead study (CLS), which is the longest continuously active prospective investigation of prenatal/early postnatal Pb exposure on human development in the world [28,30,31]. The CLS cohort of predominantly African-Americans living in Cincinnati neighborhoods in older homes with Pb contaminations without repair. As highlighted earlier, long-term exposure to heavy metal, Pb is known to have serious health consequences in the neuromuscular system and bone health. In subsequent analysis and discussion, we will present the effect of Pb exposure on the fragility of the hard tissues (bone) of the CLS female cohort.

Demographics of the CLS subjects are: mean age in years (SD): 33.10 (1.45); mean height in cm (SD): 164.56 (7.63); mean body mass in kg (SD): 92.90 (30.37); mean BMI (SD): 34.13 (10.53). The subjects were placed in four blind groups (lowest Pb exposure to the highest level: quartile-1, 2, 3, and 4) according to their blood Pb exposure levels for data analysis. According to the CDC guidelines [32], blood Pb above 5μg/dL is clinically relevant and reportable to the public health agency. The least-squares means of blood Pb groups between the highest blood Pb quartile (group 4) and the lowest blood Pb quartile (group 1) were significantly different ($p < 0.0001$). Mean blood Pb levels of all quartiles ranged between 7.37 (SD: 1.16) and 21.93 (SD: 4.64) were above the CDC guideline of acceptable blood Pb level of 5μg/dL. The University of Cincinnati provided experimental vibration response data for 90 test subjects, all of whom were adults who had all been exposed to unhealthy levels of lead as children (birth to age 78 months) [28,31].

Data Collection. Experimental time-domain subject data was extracted from two skin-mounted accelerometers attached to the skin at the lateral femoral condyle and tibial tuberosity and a force plate used by the subjects their stationary foot strike. The resonance frequency of the force plate along the excitation axis (vertical) is 1000 Hz. Subjects lift their one foot while keeping the other foot grounded and heel-strike the force plate replicating natural walking. A diagram of this setup is shown in the sensor placement schematic in Fig. 1. Low-mass, skin-mounted accelerometers were attached to the bony prominences by metal/hard Lexican holders secured on the skin with micropore tape. Previous studies by the coauthor [11,33] and others [14,34] have demonstrated that the use of low-mass accelerometers minimizes the effect of soft tissue under the accelerometers (<5% loss of accelerometer information), thereby providing a reliable measure of shock wave propagation during heel strike. Moreover, the whole-bone strength is influenced by both the trabecular structure and the cortical bone surrounding the trabecular structure [35]. Therefore, in this study, accelerometers were attached to the Femoral Condyle above-knee (AK) and below-knee (BK), giving an aggregate damping value for both trabecular and cortical bones, as shown in Fig. 1.

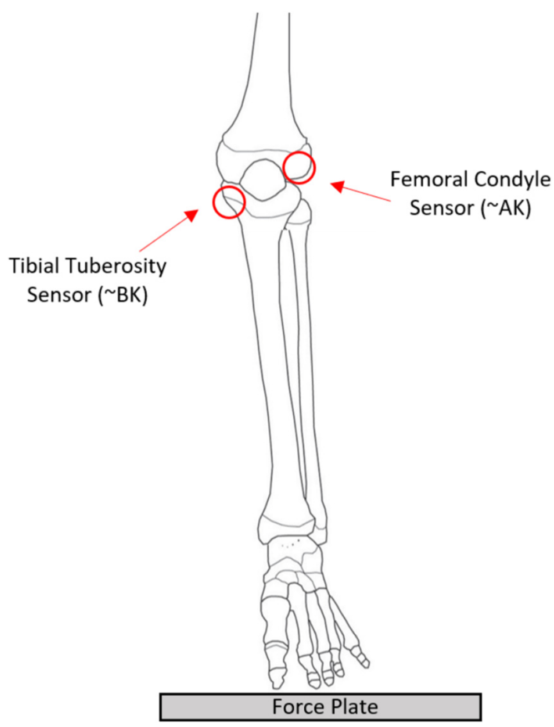


Fig. 1 Sensor placement schematic

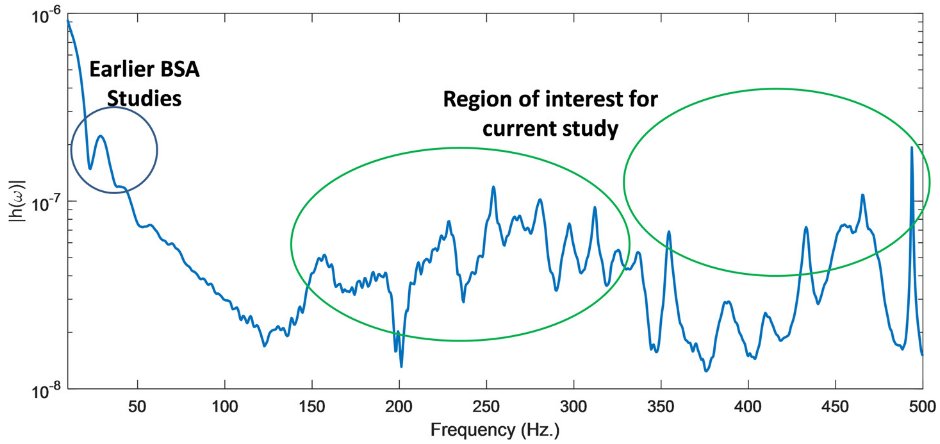
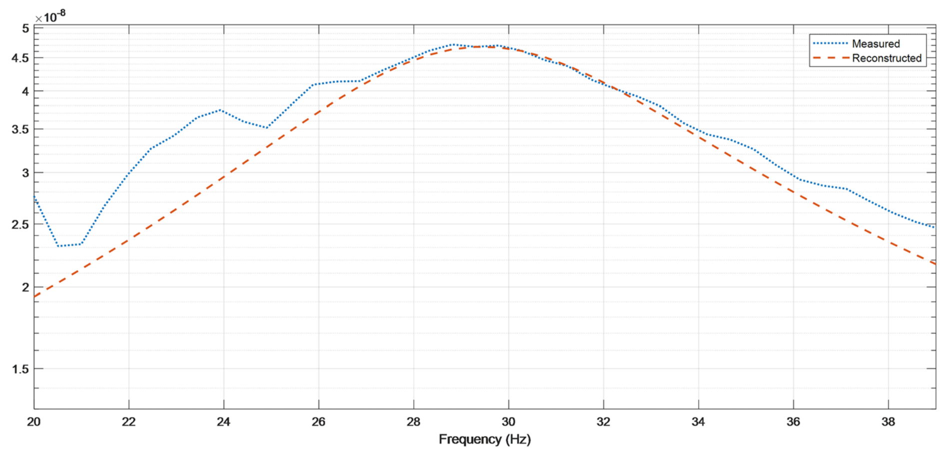
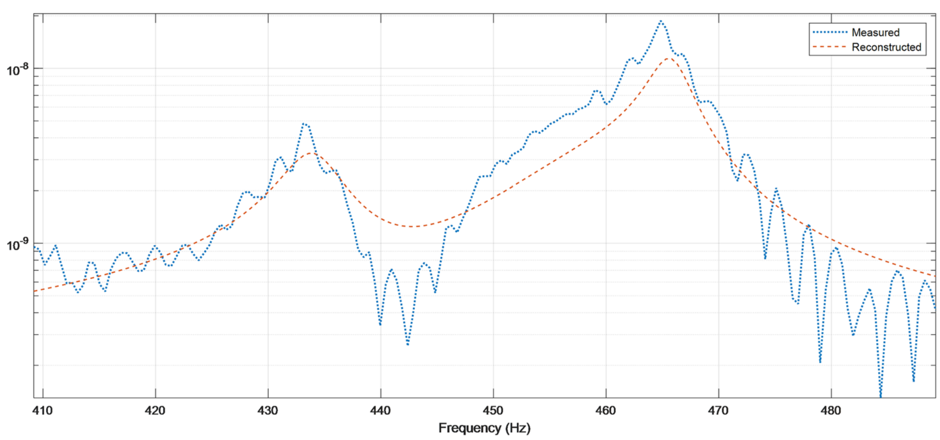


Fig. 2 Example of a typical BSA FRF



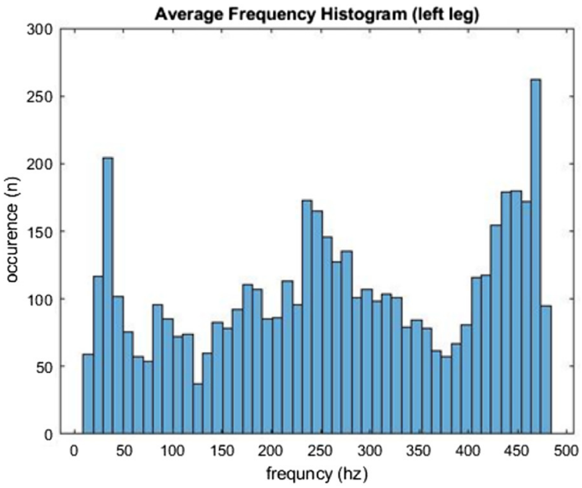
(*a*)



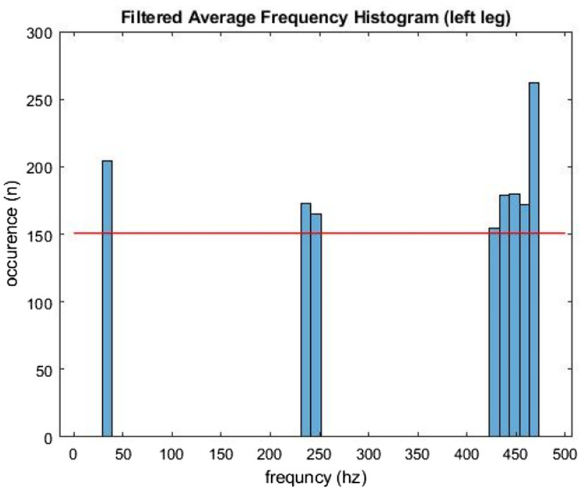
(*b*)

Fig. 3 A representative curve fit for mode pair estimation

Data from accelerometers were collected at a sampling rate of 1000 Hz, which allowed investigation of up to 500 Hz. of frequency response without any aliasing bias. Five tests (single foot strike on force plate) were performed for each subject. The time-domain signals associated with the input force $f(t)$ and the output acceleration $\ddot{x}(t)$ were converted into the frequency domain. The frequency response function (FRF) or transfer function associated with each sensor and force plate pairs was extracted using a discrete Fourier transform. A representative FRF is shown in Fig. 2 for a range of frequencies between 0 and 500 Hz. Each FRFs were curve-fitted using the Rational Fraction Polynomial (RFP) technique [36] for a specific range of frequencies. A representative curve fitting for the two frequency range is shown in Fig. 3. Stability-diagram (a modal analysis tool [36]) was used for each FRF to identify the correct number of nonspurious vibration modes (model order). We carried out stabilization analysis with 1–20 vibration modes for a selected frequency range, which allowed us to identify an accurate number of vibration modes.



(a)



(b)

Fig. 4 (*a*) Frequency histogram for the left leg, all subjects and (*b*) Filtered frequency histogram for the left leg, all subjects

This process permitted a correct curve fit toward the computation of natural frequencies and damping frequencies for the selected range of frequency by the peak picking method [37].

An individual dataset can have multiple peaks representing multiple vibration modes and their respective directions. In past studies [11,12], the damping ratio at the lowest (first) vibration mode (∼30 Hz) was considered the indicator of bone quality, while in this study, the damping ratios associated with higher-frequency vibration modes are used, as highlighted in Fig. 2. The FRFs were then divided into several smaller bins to identify the peaks in regions of differing magnitudes to identify prominent vibration modes among the subject population and filter less prominent (dominant) local peaks. These bin boundaries were placed such that the dominant vibration modes near the bin edges are preserved and not lost. Curves fit strategy, as shown in Fig. 3, was then applied to each segment of the FRF, which evaluated natural frequencies and corresponding damping ratios at each mode within the selected bin of frequency range. This process was repeated with another set of frequency-bins with differing boundaries defining upper and lower bounds of frequencies. The natural frequencies and damping ratio data from both bin sets were combined, and duplicates were removed. This approach is beneficial for subsequent statistical analysis. It allowed unique frequency/damping pairs present in both bin-sets to help capture prominent modes and higher-density regions in the combined data.

Statistical Clustering and Analysis. A histogram of natural frequency data collected from all four groups is presented in Fig. 4(*a*), indicating a prominent mode at around 30 Hz, which was the basis for past BSA studies. Additionally, prominent modes around 250 Hz and 450 Hz are also observed. By removing the frequencies below their mean value plus one standard deviation of the natural frequencies from their respective bins, three dominant modes can be identified. The filtered frequency histogram representing the dominant modes near 40, 350, and 450 Hz is shown in Fig. 4(*b*). These frequencies serve as target regions for density-based spatial clustering in determining the mean damping ratios corresponding to frequencies associated with these modes.

Density-based spatial clustering applications with noise (DBSCAN) is a clustering tool used to identify regions in a two-dimensional dataset with high spatial density, separated by lower density regions. This tool is resistant to noise, and unlike other methods such as Gaussian clustering, it does not assume the clusters to be of a specific shape [38]. For this application, DBSCAN was used to find the frequency-damping pairs that are most prevalent. For example, Fig. 5 shows representative clustering results for the tibial-tuberosity sensor for one group. This process was applied to each group and sensor combination, resulting in 16 clustering results, each identifying three modes consistent with those suggested by the frequency histograms. The means and standard deviations of the damping ratios for each cluster were then calculated. The values obtained from the left leg tibial-tuberosity sensor are shown in Table 1. A decrease in a damping ratio corresponding to an increase in frequency (denoted by modes 1, 2, and 3, respectively) is observed from the clustered data. A lower (fundamental) vibration mode of vibration captures the

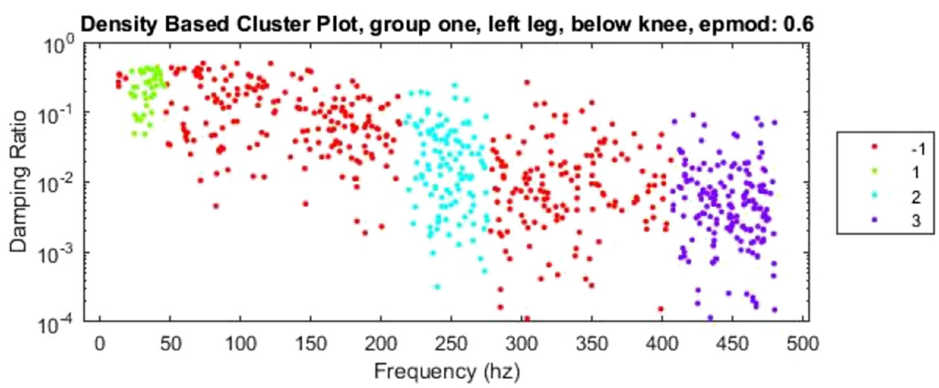


Fig. 5 Example DBSCAN results for group 1 tibial tuberosity sensor (legends 1, 2, 3 denotes the significant dense cluster of identified modes and −1 represents outliers of clustering scheme)

Table 1 Means and standard deviations of the damping ratio of the dominant mode groups associated with left leg tibial-tuberosity

Dominant modes	Group 1 (lowest blood Pb quartile)	Group 2	Group 3	Group 4 (highest blood Pb quartile)
1	0.2364 ± 0.1181	0.2202 ± 0.0982	0.2133 ± 0.1065	0.258 ± 0.1421
2	0.0339 ± 0.0447	0.0421 ± 0.0568	0.0231 ± 0.0292	0.0222 ± 0.0325
3	0.0096 ± 0.015	0.0103 ± 0.0156	0.0063 ± 0.0069	0.0085 ± 0.0128

Table 2 Pairwise ANOVA results associated with left leg tibial-tuberosity between different groups having various Pb levels

Dominant modes	Group 1 versus group 2	Group 1 versus group 3	Group 1 versus group 4	Group 2 versus group 3	Group 2 versus group 4	Group 3 versus group 4
1	0.4769	0.3402	0.4309	0.7469	0.1293	0.0903
2	0.2202	0.0457	0.0303	0.0036	0.0019	0.8486
3	0.689	0.0175	0.4626	0.0063	0.2653	0.0682

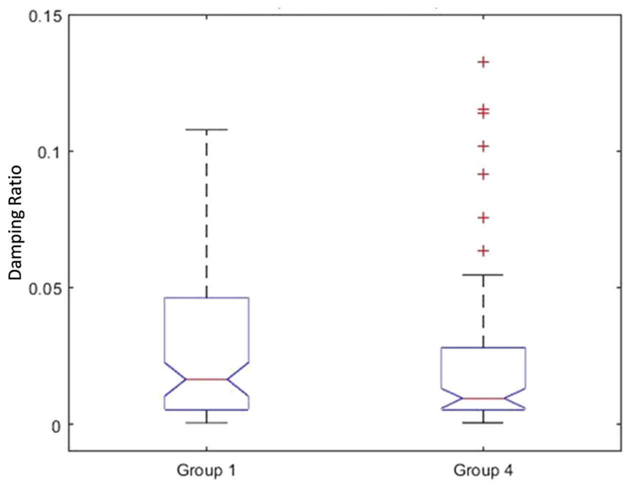


Fig. 6 Group-wise ANOVA for mode 2 for group 1 (lowest blood Pb quartile) versus Group 4 (highest blood Pb quartile) for the sensor associated with the left leg below knee (LBK)

dynamics of softer (less stiff) materials. They tend to have more energy dissipating mechanisms and hence a higher damping ratio. Higher modes characterize more rigid (stiff) material, and therefore they will have lower damping associated with it. This characteristic is observed in Table 1, which shows that the mean damping ratio associated with higher modes (mode two and mode three) is comparatively lower than that of the first mode.

To check the statistical difference between the mean damping values of three modes associated with each group having different blood Pb level exposure, ANOVA tests were carried out. Repeated group-wise one-way ANOVA first compared the mean damping values for each vibration mode. This process was conducted independently at each of the four sensor locations: above the right knee, below the right knee, above the left knee, and below the left knee, necessitating 72 total comparisons; one for each group, sensor, and mode combination. A statistically significant decrease ($p \leq 0.05$) for 21 out of the 72 comparisons was identified. The higher p-values signify the null hypothesis that there is no difference in damping ratio among the groups having different Pb levels. A p-value less than 0.05 ($p \leq 0.05$) corresponds to a 95% confidence interval, and it rejects the null hypothesis indicating a significant difference in damping ratio among two different groups. A representative p-values of the comparisons for the left leg's tibial-tuberosity sensor are presented in Table 2. The p-values at the second and third modes are generally lower than those at the first mode, indicating that the higher frequencies provide a better basis for identifying discrepancies in bone quality measures (in our case, damping ratio). It can be observed from Table 2 that the p-values associated with second and third vibration modes are lower for some group pairs, and except for one set of pair, the p-values of the first mode are higher than those of the second mode. For each group pair, the lower p-values among the three dominant modes suggest that the higher frequencies provide a better basis for identifying discrepancies (significant statistical difference) in bone quality measures (in our case, damping ratio).

Moreover, observations between the paired groups also highlight the significant statistical difference between different blood Pb level groups. For example, a representative group-wise comparison is shown in Fig. 6. A decrease of 0.0117 in the mean damping ratio corresponding to the second mode from group 1 (lowest blood-lead) to group 4 (highest blood lead) is observed in Figure with a p value of 0.0303, highlighting a significant difference between their damping ratio. For the second mode, similar trends ($p < 0.05$) can be seen between other group pairs (group 1-group 3, group 2-Group3, and group 2-group 4). These results support our hypothesis correlating the damping ratio associated with the higher modes and varying blood Pb levels exposure.

Conclusion

This research summarizes the data about the impact of early life Pb exposure on the bone fragility and potential risk of fracture among African American women in the CLS cohort. The damping capacity among subject groups with varying Pb exposure levels groups is investigated through a systematic clustering and statistical analysis of clinical BSA data. A decrease in a damping ratio corresponding to an increase in frequency (higher vibration modes) was observed for all groups representing lower damping capacity of the stiffer section (bones). Statistical analysis demonstrates differences in the damping ratio among the patient groups with different blood Pb levels. For example, it can be observed that the damping ratios associated with the second mode have a statistical correlation with the varying blood Pb level exposure. This observation supports our hypothesis that higher frequency and damping ratio may be treated as bone fragility degradation measures. Differences in such degradation may contribute to some health conditions (in this study, different Pb level exposure). It is also observed that measurements are taken from the right-leg generally exhibit lower p-values than those obtained from the left leg. This discrepancy may be attributed to the manual identification of the frequency-damping pairs (peak picking method). Another explanation may be contributed to observation in Ref. [39] that approximately 81% prevalence of right leg dominance in humans, resulting in differences in skeletal muscles between right and left legs. Future research in this area may involve multiple tri-axial accelerometers on the lower body to identify different directional modes of vibration (axial, transverse, or lateral) and their associated damping capacity. Animal models of clinical BSA tests have shown that knee joint (50%) and bone plus skin (38%+12%) have the top two contributions to the damping capacities of the musculoskeletal system [40]. Other factors, such as noncollagenous proteins (Osteopontin), also play an essential role in the dissipation of mechanical energy when subjected to load [41]. Hence, future human studies are needed to noninvasively investigate the impact of different factors (Pb, Osteopontin, etc.) on the relative damping capacities of various musculoskeletal segments. More studies involving damping ratio associated with a range of natural frequencies and their correlation with health measures may help realize the use of noninvasive wearable technologies for the future, which may serve as useful indicators and precursors for bone health quality.

Acknowledgment

The BSA technology used in this study is a patented device under coauthor Bhattacharya and Watts (Patent: 2014-Serial No. 12/402,586).

Funding Data

- NIEHS (No. 1R01ES024074-01; Funder ID: 10.13039/100000066).

References

[1] Van der Perre, G., Van Audekercke, R., Martens, M., and Mulier, J. C., 1983, “Identification of in-Vivo Vibration Modes of Human Tibiae by Modal Analysis,” ASME J. Biomed. Eng., **105**(3), pp. 244–248.

[2] Cornelissen, P., Cornelissen, M., Van der Perre, G., Christensen, A. B., Ammitzbøll, F., and Dyrbye, C., 1986, “Assessment of Tibial Stiffness by Vibration Testing in Situ—II. Influence of Soft Tissues, Joints and Fibula,” J. Biomech., **19**(7), pp. 551–561.

[3] Lowet, G., Van Audekercke, R., Van der Perre, G., Geusens, P., Dequeker, J., and Lammens, J., 1993, “The Relation Between Resonant Frequencies and Torsional Stiffness of Long Bones In Vitro. Validation of a Simple Beam Model,” J. Biomech., **26**(6), pp. 689–696.

[4] Van der Perre, G., and Lowet, G., 1996, “In Vivo Assessment of Bone Mechanical Properties by Vibration and Ultrasonic Wave Propagation Analysis,” Bone, **18**(1), pp. S29–S35.

[5] Nikiforidis, G., Bezerianos, A., Dimarogonas, A., and Sutherland, C., 1990, “Monitoring of Fracture Healing by Lateral and Axial Vibration Analysis,” J. Biomech., **23**(4), pp. 323–330.

[6] Bediz, B., Özgüven, H. N., and Korkusuz, F., 2010, “Vibration Measurements Predict the Mechanical Properties of Human Tibia,” Clin. Biomech., **25**(4), pp. 365–371.

[7] Campoli, G., Baka, N., Kaptein, B. L., Valstar, E. R., Zachow, S., Weinans, H., and Zadpoor, A. A., 2014, “Relationship Between the Shape and Density Distribution of the Femur and Its Natural Frequencies of Vibration,” J. Biomech., **47**(13), pp. 3334–3343.

[8] Yassine, R., Fakhreddine, A., Sayegh, M., Mustapha, S., and Hamade, R. F., 2018, “Dynamic Assessment and Modeling of the Modal Frequencies and Shapes of Bovine Tibia,” ASME J Nondestruct. Eval.,” **1**(4), p. 041006.

[9] Nakatsuchi, Y., Tsuchikane, A., and Nomura, A., 1996, “The Vibrational Mode of the Tibia and Assessment of Bone Union in Experimental Fracture Healing Using the Impulse Response Method,” Med. Eng. Phys., **18**(7), pp. 575–583.

[10] Christopoulou, G. E., Stavropoulou, A., Anastassopoulos, G., Panteliou, S. D., Papadaki, E., Karamanos, N. K., and Panagiotopoulos, E., 2006, “Evaluation of Modal Damping Factor as a Diagnostic Tool for Osteoporosis and Its Relation With Serum Osteocalcin and Collagen I N-Telopeptide for Monitoring the Efficacy of Alendronate in Ovariectomized Rats,” J. Pharm. Biomed. Anal., **41**(3), pp. 891–897.

[11] Bhattacharya, A., Watts, N. B., Davis, K., Kotowski, S., Shukla, R., Dwivedi, A. K., and Coleman, R., 2010, “Dynamic Bone Quality: A Non-Invasive Measure of Bone’s Biomechanical Property in Osteoporosis,” J. Clin. Densitom., **13**(2), pp. 228–236.

[12] Bhattacharya, A., Watts, N. B., Dwivedi, A., Shukla, R., Mani, A., and Diab, D., 2016, “Combined Measures of Dynamic Bone Quality and Postural Balance—A Fracture Risk Assessment Approach in Osteoporosis,” J. Clin. Densitom., **19**(2), pp. 154–164.

[13] Nelson, M. L., Cox, C., Altman, L., Khoury, J., Bhattacharya, A., and Wasserman, H., 2020, “Bone Shock Absorption in Pediatric Patients With Osteogenesis Imperfecta – a Pilot Study to Assess the Potential of This Technique to Detect Differences in Bone Fragility,” J. Clin. Densitom., **23**(4), pp. 685–689.

[14] Ziegert, J. C., and Lewis, J. L., 1979, “The Effect of Soft Tissue on Measurements of Vibrational Bone Motion by Skin-Mounted Accelerometers,” ASME J. Biomech. Eng., **101**(3), pp. 218–220.

[15] Thomsen, J. J., 1990, “Modelling Human Tibia Structural Vibrations,” J. Biomech., **23**(3), pp. 215–228.

[16] Trama, R., Hautier, C., and Blache, Y., 2020, “Input and Soft-Tissue Vibration Characteristics Sport-Specific Tasks,” Med. Sci. Sports Exerc., **52**(1), pp. 112–119.

[17] Tarragó, O., and Brown, M. J., 2017, “Case Studies in Environmental Medicine (CSEM): Lead Toxicity (Course: WB2832),” Agency for Toxic Substances and Disease Registry (ATSDR), accessed Apr. 21, 2021, https://www.atsdr.cdc.gov/csem/csem.asp?csem=34&po=10

[18] Ris, M. D., Dietrich, K. N., Succop, P. A., Berger, O. G., and Bornschein, R. L., 2004, “Early Exposure to Lead and Neuropsychological Outcome in Adolescence,” J. Int. Neuropsychol. Soc., **10**(2), pp. 261–270.

[19] Yuan, W., Holland, S. K., Cecil, K. M., Dietrich, K. N., Wessel, S. D., Altaye, M., Hornung, R. W., Ris, M. D., Egelhoff, J. C., and Lanphear, B. P., 2006, “The Impact of Early Childhood Lead Exposure on Brain Organization: A Functional Magnetic Resonance Imaging Study of Language Function,” Pediatrics, **118**(3), pp. 971–977.

[20] Cecil, K. M., Dietrich, K. N., Altaye, M., Egelhoff, J. C., Lindquist, D. M., Brubaker, C. J., and Lanphear, B. P., 2011, “Proton Magnetic Resonance Spectroscopy in Adults With Childhood Lead Exposure,” Environ. Health Perspect., **119**(3), pp. 403–408.

[21] Silbergeld, E. K., Sauk, J., Somerman, M., Todd, A., McNeill, F., Fowler, B., Fontaine, A., and Van Buren, J., 1993, “Lead in Bone: Storage Site, Exposure Source, and Target Organ,” Neurotoxicology, **14**(2–3), pp. 225–236.

[22] Pounds, J. G., Long, G. J., and Rosen, J. F., 1991, “Cellular and Molecular Toxicity of Lead in Bone,” Environ. Health Perspect., **91**, pp. 17–32.

[23] Shukla, R., Dietrich, K. N., Bornschein, R. L., Berger, O., and Hammond, P. B., 1991, “Lead Exposure and Growth in the Early Preschool Child: A Follow-Up Report From the Cincinnati Lead Study,” Pediatrics, **88**(5), pp. 886–892.

[24] Zuscik, M. J., Pateder, D. B., Edward Puzas, J., Schwarz, E. M., Rosier, R. N., and O’Keefe, R. J., 2002, “Lead Alters Parathyroid Hormone-Related Peptide and Transforming Growth Factor-β1 Effects and AP-1 and NF-κKB Signaling in Chondrocytes,” J. Orthop. Res., **20**(4), pp. 811–818.

[25] Popovic, M., McNeill, F. E., Webber, C. E., and Chettle, D. R., 2004, “The Effect of Lead in Bone Densitometry,” Nucl. Instrum. Methods Phys. Res. Sect. B, **213**, pp. 599–602.

[26] Chia, S. E., Chua, L. H., Ng, T. P., Foo, S. C., and Jeyaratnam, J., 1994, “Postural Stability of Workers Exposed to Lead,” Occup. Environ. Med., **51**(11), pp. 768–771.

[27] Yokoyama, K., Araki, S., Yamashita, K., Murata, K., Nomiyama, K., Nomiyama, H., Tao, Y. X., and Liu, S. J., 2002, “Subclinical Cerebellar Anterior Lobe, Vestibulo-Cerebellar and Spinocerebellar Afferent Effects in Young Female Lead Workers in China: Computerized Posturography With Sway Frequency Analysis and Brainstem Auditory Evoked Potentials,” Ind. Health, **40**(3), pp. 245–253.

[28] Bhattacharya, A., Shukla, R., Dietrich, K. N., and Bornschein, R. L., 2006, “Effect of Early Lead Exposure on the Maturation of Children’s Postural Balance: A Longitudinal Study,” Neurotoxicol. Teratol., **28**(3), pp. 376–385.

[29] Kincl, L. D., Dietrich, K. N., and Bhattacharya, A., 2006, “Injury Trends for Adolescents With Early Childhood Lead Exposure,” J. Adolescent Health, **39**(4), pp. 604–606.

[30] Dietrich, K. N., Berger, O. G., Succop, P. A., Hammond, P. B., and Bornschein, R. L., 1993, “The Developmental Consequences of Low to Moderate Prenatal and Postnatal Lead Exposure: Intellectual Attainment in the Cincinnati Lead Study Cohort Following School Entry,” Neurotoxicol. Teratol., **15**(1), pp. 37–44.

[31] Dietrich, K. N., Succop, P. A., and Berger, O. G., 1993, “Lead Exposure and the Motor Developmental Status of Urban Six-Year-Old Children in the Cincinnati Prospective Study,” Pediatrics, **91**(2), pp. 301–307.

[32] Advisory Committee on Childhood Lead Poisoning Prevention, U.S. Centers for Disease Control and Prevention, 2012, “Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention,” Advisory Committee on Childhood Lead Poisoning Prevention, U.S. Centers for Disease Control and Prevention, accessed Apr. 21, 2021, https://www.cdc.gov/nceh/lead/acclpp/final_document_030712.pdf

[33] Huang, S., and Bhattacharya, A., 1993, “The Effects of Osteoarthritis on the Biomechanical Properties of the Tibia,” Chin. J. Med. Biol. Eng., **13**(3), pp. 255–264.

[34] Saha, S., and Lakes, R. S., 1977, “The Effect of Soft Tissue on Wave-Propagation and Vibration Tests for Determining the In Vivo Properties of Bone,” J. Biomech., **10**(7), pp. 393–401.

[35] Stenström, M., Olander, B., Lehto-Axtelius, D., Madsen, J. E., Nordsletten, L., and Carlsson, G. A., 2000, “Bone Mineral Density and Bone Structure Parameters as Predictors of Bone Strength: An Analysis Using Computerized Microtomography and Gastrectomy-Induced Osteopenia in the Rat,” J. Biomech., **33**(3), pp. 289–297.

[36] Ewins, D. J., 1984, *Modal Testing: Theory and Practice*, Vol. 15, Research Studies Press, Letchworth, UK.

[37] Brandt, A., 2011, *Noise and Vibration Analysis: Signal Analysis and Experimental Procedures*, Wiley, Hoboken, NJ.

[38] Schubert, E., Sander, J., Ester, M., Kriegel, H. P., and Xu, X., 2017, “DBSCAN Revisited, Revisited: Why and How You Should (Still) Use DBSCAN,” ACM Trans. Database Syst., **42**(3), pp. 1–21.

[39] Porac, C., and Coren, S., 1981, *Lateral Preferences and Human Behavior*, Springer-Verlag, New York, pp. 181–191.

[40] Dodge, T., Wanis, M., Ayoub, R., Zhao, L., Watts, N. B., Bhattacharya, A., Akkus, O., Robling, A., and Yokota, H., 2012, “Mechanical Loading, Damping, and Load-Driven Bone Formation in Mouse Tibiae,” Bone, **51**(4), pp. 810–818.

[41] Fantner, G. E., Adams, J., Turner, P., Thurner, P. J., Fisher, L. W., and Hansma, P. K., 2007, “Nanoscale Ion Mediated Networks in Bone: Osteopontin Can Repeatedly Dissipate Large Amounts of Energy,” Nano Letters, **7**(8), pp. 2491–2498.